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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Darko FILIC et al. **PCT Branch**

Appl. No. : Not Yet Assigned (U.S. National Phase of PCT/HR2003/000036)

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For : PROCESS FOR THE PREPARATION OF MODIFICATION I OF N-(1-METHYLETHYLAMINOCARBONYL)-4-(3-METHYLPHENYLAMINO)-3-PYRIDINESULFONAMIDE

CLAIM OF PRIORITY

Commissioner for Patents
U.S. Patent and Trademark Office
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Randolph Building
401 Dulany Street

Sir:

Applicant hereby claims the right of priority granted pursuant to 35 U.S.C. 119 and 365 based upon Croatian Application No. P20020603A, filed July 19, 2002. The International Bureau already should have sent a certified copy of the Croatian application to the United Stated designated office. If the certified copy has not arrived, please contact the undersigned.

A verified English language translation of the Croatian application is being submitted herewith.

Respectfully submitted,
Darko FILIC et al.

Neil F. Greenblum
Reg. No. 28,394

Arnold Turk
Reg. No. 33,094

January 17, 2005
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

277/2004

I, the undersigned Vera Lamut, Permanent Court Interpreter for the English language, appointed by the decree of the Secretariat of Justice and General Administration of the Socialist Republic Slovenia in Ljubljana No. G.Z. P 74/A-9/71 of 14 September 1971, declare hereby that I am conversant with the English and Croatian languages and that the attached translation was made by me and is true and complete to the best of my knowledge and belief and I further declare that it entirely corresponds to the priority document of the Croatian patent application P20020603A of 17 July 2002.

Ljubljana, 28 December 2004

Vera Lamut

NEW PROCESS FOR THE PREPARATION OF MODIFICATION I OF *N*-(1-METHYLETHYLAMINOCARBONYL)-4-(3-METHYLPHENYLAMINO)-3-PYRIDINESULFONAMIDE

International Patent Classification: C 07 D 213/70; A 61 K 31/44

The present invention relates to the preparation of modification I of *N*-(1-methylethyl aminocarbonyl)-4-(3-methylphenylamino)-3-pyridinesulfonamide (in the further text of the application designated by its generic name "torasemide").

Torasemide is a new potent diuretic in the class of so-called "loop" diuretics and is described in DE patent 25 16 025 (Example 71) as 3-isopropylcarbamylsulfonamide-4-(3'-methyl)-phenylamino pyridine. Structurally, it is completely different from diuretics of the same class such as e.g. furosemide, bumetanide and azosemide. Besides diuretic properties it also possesses antihypertensive ones.

As a diuretic of Henle's loop it is interesting as an agent for preventing heart or heart tissue damages caused by metabolic or ionic abnormalities associated with ischemia, in the treatment of thrombosis, angina pectoris, asthma, hypertension, nephroedema, pulmonary edema, primary and secondary aldosteronism, Bartter's syndrome, tumours, glaucoma, decrease of intraocular pressure, acute or chronic bronchitis, in the treatment of cerebral edema caused by trauma, ischemia, concussion of the brain, metastases or epileptic attacks and in the treatment of nasal infections caused by allergens.

Hitherto, some crystal modifications of torasemide have been known: modification I [*Acta Cryst.* B**34** (1978), 1304-1310], modification II [*Acta Cryst.* B**34** (1978), 2659-2662], modification III (US patent 6,166,045), modification N (US patent 6,399,637), modification V (PLIVA; PCT/WO 01/87841), modification V (TEVA; PCT/WO 01/10441), as well as an amorphous modification of PLIVA (PCT/WO 01/70694), an amorphous modification of TEVA (PCT/WO 01/10441) and Dupont 2 solvate adducts (PCT/WO 01/10441). Crystal modifications I, II and N differ in single cell

parameters, which is confirmed by X-ray diffraction on their monocrystals. Modification I with melting point 169 °C [*Acta Cryst.* B**34** (1978), 1304-1310] and modification N with melting point 165 °C [US patent 6,399,637; *Croat. Chem. Acta* **74** (2001) 103-120] crystallize in the monoclinic space group $P2_1/c$ (prisms), while modification II with melting point 162 °C crystallizes in the monoclinic space group P2/n (foils) [*Acta Cryst.* B**34** (1978), 2659-2662].

It is known that modification I of torasemide and modification II of torasemide crystallize simultaneously when a torasemide solution in a solvent mixture petroleum ether/ethanol slowly evaporates [*Acta Cryst.* B**34** (1978), 1304-1310]. Such a manner of preparation, however, wherein both modifications crystallize from the same solvent mixture and hence must be separated with regard to their macroscopic crystal form, is certainly not suitable for large-scale production.

Further, in the patent application PCT/WO 01/10441 there is described the preparation of modification I of torasemide by recrystallization from methanol of modification II of torasemide or of a mixture of modifications I and II of torasemide or of modification V (TEVA) of torasemide or of Dupont Form 2 solvate adducts of torasemide as well as of their mixtures.

Contrary to the above, in the text of patents US 4,743,693; US reissue 34,580; US 4,822,807; US reissue 34,672; US 5,914,336 and US 6,166,045 it is stated that by recrystallization from solvents always modification II of torasemide is formed. In addition, it is known that by heating torasemide in most solvents its irreversibile decomposition takes place (US 4,743,693; US reissue 34,580; US 4,822,807; US reissue 34,672), whereby the content of accompanying impurities is increased. In view of these statements, recrystallization is not suitable method for the preparation of modification I of torasemide.

The patents US 4,743,693 and US reissue 34,580 protect a process for the preparation of modification I of torasemide, wherein a suspension of modification II of torasemide prepared according to patent DE 25 16 025 in water is stirred under the addition of a catalytic amount of modification I of torasemide (0.1 %) at a temperature from room

temperature to 90 °C within 3 hours to 14 days. It is stated that no decomposition of torasemide takes place. The patent application PCT/WO 01/10441 discloses the preparation of modification I of torasemide by stirring modification II of torasemide or a mixture of modifications I and II of torasemide in a solvent mixture containing acetonitrile under reflux, or in a mixture of DMSO : acetonitrile at a temperature from 20 °C to 30 °C within 30 to 45 minutes or in a solvent mixture of water : acetonitrile at a temperature from 40 °C to 60 °C over a period of more than 45 minutes. In the same patent application also the preparation of modification I of torasemide by stirring Dupont Form 2 of torasemide in water at pH 5 and at room temperature or by stirring modification II of torasemide in ethanol or dimethylformamide also at room temperature is disclosed.

From the text of patents US 4,743,693; US reissue 34,580; US 4,822,807; US reissue 34,672; US 5,914,336 and US 6,166,045 it is evident that by the preparation and conventional purification of crude torasemide either by precipitation or by recrystallization from solvents the modification II of torasemide is obtained.

In our further investigations in the torasemide field we have surprisingly found a new, hitherto not known process for the preparation of modification I of torasemide.

The new process for the preparation of modification I of torasemide comprises the preparation of modification I of torasemide by directly acidifying an alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide. The preparation process of the invention enables a more effective, more rapid and economically more acceptable method for the preparation of modification I of torasemide.

According to the process of the invention, for the preparation of the alkaline extract of the original reaction mixture of last phase in the synthesis of torasemide there can be used water solutions of alkaline hydroxides such as solutions of lithium, sodium and potassium hydroxide as well as water solutions of alkaline carbonates such as solutions of sodium and potassium carbonate.

According to the present process, the acidifiying of the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide can be performed with inorganic acids such as hydrochloric, sulfuric, phosphoric and nitric acids and with organic acids such as formic, acetic, propionic, oxalic, tartaric, methanesulfonic and *p*-toluenesulfonic acids and carbon dioxide.

The acidifiying of the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide is performed by a continuous addition of the acid under stirring at a stirrer rate from 10 to 300 r/min within 5 minutes to 24 hours until a pH from about 8.5 to about 5.0, most preferably from about 7.5 to about 7.0 is reached, which depends on the acid/base concentration as well as on the batch size, the volume, the construction and the geometry of the reactor. During the addition of the acid it is not necessary to avoid local high concentrations of the acid. The acidifying is performed at temperatures from about 0 °C to about 50 °C, most preferably at room temperature.

After reaching the desired pH, the suspension is stirred for another 10 to 240 minutes at a temperature from about 0 to about 50 °C, most preferably at room temperature, in order to complete the crystallization. The crystals are separated from the water medium in a usual manner such as filtration, and then dried down to a low moisture content, most preferably below 0.5 %.

It has been found that by using of the process of the present invention no decomposition of torasemide occurs, modification I of torasemide contains the remaining solvents within pharmacopeic limits and the impurities that are possibly present in the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide pass into the bases, which means that a chemically pure modification I of torasemide is obtained.

Moreover, it has been found that the stable modification I of torasemide prepared according to the process of the present invention is obtained in a "free flow" form, i.e. suitable for the preparation of pharmaceutical forms such as tablets, capsules or injections.

The present invention is illustrated but in no way limited by the following Examples.

Example 1

The original reaction mixture of the last phase in the synthesis of torasemide (starting from 100 g of 4-hydroxy-3-pyridinesulfonic acid) was treated with an about 10 % aqueous solution of sodium hydroxide. To the alkaline solution an about 10 % aqueous acetic acid solution was continuously added within 30 minutes at room temperature under a stirring rate of about 50 r/min to reach pH 7.0. Then the obtained suspension was stirred for further 30 minutes at the same temperature. The crystals were sucked off and washed with water, whereupon, after drying in a vacuum dryer to a constant weight, 100 g of modification I of torasemide were obtained.

Content according to HPLC 99.2 %, moisture < 0.2 %

The IR spectrum and the X-ray powder pattern of the thus obtained sample of modification I of torasemide corresponded to the IR spectrum and the X-ray powder pattern of an authentic sample of modification I of torasemide obtained according to *Acta Cryst.* B**34** (1978), 1304-1310.

Example 2

The original reaction mixture of the last phase in the synthesis of torasemide (starting from 10.0 kg of 4-hydroxy-3-pyridinesulfonic acid) was treated with an about 2.5 % aqueous solution of sodium hydroxide. To the solution an about 5 % aqueous hydrochloric acid solution was added within 60 minutes at room temperature under a stirring rate of about 200 r/min to reach pH 7.1-7.2. Then the obtained suspension was stirred for further 60 minutes at the same temperature. The crystals were sucked off and washed with water, whereupon, after drying in a vacuum dryer up to a constant weight, 11.0 kg of a stable modification I of torasemide were obtained.

Content according to HPLC 99.1 %, moisture 0.3 %

The IR spectrum and the X-ray powder pattern of the thus obtained sample of modification I of torasemide corresponded to the IR spectrum and the X-ray powder pattern of an authentic sample of modification I of torasemide obtained according to *Acta Cryst.* B**34** (1978), 1304-1310.

Claims

1. Process for the preparation of modification I of torasemide, characterized in that an alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide is subjected to controlled acidifying with inorganic or organic acids.

2. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the modification I of torasemide is chemically pure.

3. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the modification I of torasemide contains less than 0.5 % of water.

4. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the modification I contains remaining solvents within pharmacopeic limits.

5. Process for the preparation of modification I of torasemide according to claim 1, characterized in that for the preparation of the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide water solutions of lithium, sodium and potassium hydroxide and water solutions of sodium and potassium carbonate are used.

6. Process for the preparation of modification I of torasemide according to claim 1, characterized in that for acidifying the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide inorganic acids such as hydrochloric, sulfuric, phosphoric and nitric acids or organic acids such as formic, acetic, propionic, oxalic, tartaric, methanesulfonic or *p*-toluenesulfonic acid are used.

7. Process for the preparation of modification I of torasemide according to claim 1, characterized in that for acidifying the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide carbon dioxide is used.

8. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out up to a pH from about 8.5 to about 5.0.

9. Process for the preparation of modification I of torasemide according to claim 8, characterized in that the acidifying is carried out up to a pH from about 7.5 to about 7.0.

10. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out at a stirrer rate from 10 r/min to 300 r/min.

11. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out within 5 minutes to 24 hours.

12. Process for the preparation of modification I of torasemide according to claim 11, characterized in that the acidifying is carried out continuously.

13. Process for the preparation of modification I of torasemide according to claims 11 and 12, characterized in that the acidifying is carried out without avoiding high local acid concentrations.

14. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out at a temperature from 0 °C to 50 °C.

15. Process for the preparation of modification I of torasemide according to claim 14, characterized in that the acidifying is carried out at room temperature.

16. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the suspension obtained after acidifying and reaching the desired pH is stirred from 10 minutes to 240 minutes.

17. Process for the preparation of modification I of torasemide according to claim 16, characterized in that the suspension obtained after acidifying and reaching the desired pH is stirred at a temperature from 0 °C to 50 °C.

18. Process for the preparation of modification I of torasemide according to claim 17, characterized in that the suspension obtained after acidifying and reaching the desired pH is stirred at room temperature.

Abstract

The present invention relates to a new process for the preparation of modification I of torasemide by precipitation with acids from an alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide.

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Državnom zavodu za intelektualno vlasništvo podnesena je prijava patenta s podacima kako slijedi:
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(71) Ime(na) podnositelja prijave ili tvrtka i sjedište: */ Name(s) of applicants:*

Pliva d.d.
Ulica grada Vukovara 49
10000 Zagreb, HR

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(54) Naziv izuma: */ Title of the invention:*

NOVI POSTUPAK ZA PRIPRAVU MODIFIKACIJE I N-(1-METILETILAMINOKARBONIL)-4-(3-METILFENILAMINO)-3-PIRIDINSULFONAMIDA

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NOVI POSTUPAK ZA PRIPRAVU MODIFIKACIJE I *N*-(1-METILETILAMINOKARBONIL)-4-(3-METILFENILAMINO)-3-PIRIDINSULFONAMIDA

OPIS IZUMA

C 07 D 213/70
A 61 K 31/44

Izum se odnosi na pripravu modifikacije I *N*-(1-metiletilamino-karbonil)-4-(3-metilfenilamino)-3-piridinsulfonamida (u daljnjem se tekstu navodi pod generičkim imenom "torasemid").

Torasemid je novi potentni diuretik u klasi tzv. "loop diuretika", a opisan je u primjeru 71 izuma DE 25 16 025 kao 3-izopropilkarbamilsulfonamid-4-(3'-metil)-fenilamino piridin. Strukturno se potpuno razlikuje od diuretika iz iste klase kao što su npr. furosemid, bumetanid i azosemid. Pored diuretskih posjeduje i antihipertenzivna svojstva.

Kao diuretik Henleove petlje zanimljiv je kao sredstvo za zaštitu srca ili srčanog tkiva od oštećenja uzrokovanih metaboličkim ili ionskim abnormalnostima povezanim sa ishemijom, pri tretiranju tromboze, angine pektoris, astme, hipertenzije, nefroedema, pulmonalnog edema, primarnog ili sekundarnog aldosteronizma, Bartterovog sindroma, tumora, glaukoma, sniženja intraokularnog tlaka, akutnog ili kroničnog bronhitisa, pri tretiranju cerebralnih edema uzrokovanih traumom, ishemijom, potresom mozga, metastazama ili epileptičnim napadajima, te pri tretiranju nazalnih infekcija uzrokovanih alergenima.

Do danas je poznato nekoliko kristalnih modifikacija torasemida: modifikacija I [*Acta Cryst.* **B34**, (1978) 1304-1310], modifikacija II [*Acta Cryst.* **B34**, (1978) 2659-2662], modifikacija III (US patent 6,166,045), modifikacija N (US patent 6,399,637), modifikacija V (PLIVA; PCT/WO 01/87841), modifikacija V (TEVA; PCT/WO 01/10441), zatim amorfna modifikacija PLIVA (PCT/WO 01/70694) i amorfna modifikacija TEVA (PCT/WO 01/10441) te Dupont 2 solvatni adukti (PCT/WO 01/10441). Kristalne modifikacije I, II i N razlikuju se prema parametrima jedinične ćelije, što je utvrđeno difrakcijom rentgenskih zraka na njihovim monokristalima. Modifikacija I s talištem 169 °C [*Acta Cryst.* **B34**, (1978) 1304-1310] i modifikacija N s talištem 165 °C [US patent 6,399,637; *Croat. Chem. Acta* 74 (2001) 103-120], kristaliziraju u monoklinskoj prostornoj grupi $P2_1/c$ (prizme), dok modifikacija II s talištem 162 °C kristalizira u monoklinskoj prostornoj grupi P2/n (listići) [*Acta Cryst.* **B34**, (1978) 2659-2662].

Poznato je da modifikacija I torasemida i modifikacija II torasemida simultano kristaliziraju kada otopina torasemida u smjesi otapala petroleter/etanol polako hlapi [*Acta Cryst.* **B34**, (1978) 1304-1310]. Ovakav način priprave pri kojem obje modifikacije kristaliziraju iz iste smjese otapala te ih je potrebno odvajati, s obzirom na njihov makroskopski kristalni oblik, svakako nije pogodan za pripravu u uvećanom mjerilu.

Nadalje, u patentnoj prijavi PCT/WO 01/10441 opisana je priprava modifikacije I torasemida prekristalizacijom modifikacije II torasemida, ili smjese modifikacija I i II torasemida, ili modifikacije V (TEVA) torasemida ili Dupont forme 2 solvatnih adukata torasemida kao i njihovih smjesa iz metanola.

Za razliku od navedenog, u tekstu patenata US 4,743,693; US Re 34,580; US 4,822,807; US Re 34,672; US 5,914,336 i US 6,166,045 navodi se da prekristalizacijom iz otapala uvijek nastaje modifikacija II torasemida. Dodatno, poznato je da prilikom zagrijavanja torasemida u većini otapala dolazi do njegovog ireverzibilnog raspada (US 4,743,693; US Re 34,580; US 4,822,807; US Re 34,672) pri čemu se povećava sadržaj pratećih onečišćenja. Obzirom na navedeno prekristalizacija nije pogodna metoda za pripravu modifikacije I torasemida.

Patentima US 4,743,693 i US Re. 34,580 zaštićen je postupak priprave modifikacije I torasemida tako, da se suspenzija modifikacije II torasemida, pripravljena u skladu s patentom DE 25 16 025, u vodi uz dodatak katalitičke količine modifikacije I torasemida (0,1 %) miješa, pri temperaturama od sobne do 90°C, tijekom 3 sata do 14 dana. Naznačeno je da pri tome ne dolazi do raspada torasemida. Patentna prijava PCT/WO 01/10441 opisuje pripravu modifikacije I torasemida miješanjem modifikacije II torasemida ili smjese modifikacija I i II torasemida u smjesi otapala koja sadrži acetonitril, pri refluksu, ili u smjesi DMSO:acetonitril pri temperaturama od 20°C do 30°C tijekom 30 do 45 minuta, odnosno u smjesi otapala voda:acetonitril pri temperaturama od 40°C do 60°C tijekom više od 45minuta. U istoj patentnoj prijavi opisuje se i priprava modifikacije I torasemida miješanjem Dupont forme 2 torasemida u vodi pri pH 5 i pri sobnoj temperaturi, odnosno miješanjem modifikacije II torasemida u etanolu ili dimetilformamidu također pri sobnoj temperaturi.

Iz teksta patenata US 4,743,693; US Re 34,580; US 4,822,807; US Re 34,672, US 5,914,336 i US 6,166,045 saznajemo da se pripravom i uobičajenim pročišćavanjem sirovog torasemida, bilo precipitacijom bilo prekristalizacijom iz otpala, dobiva modifikacija II torasemida.

U nastavku naših istraživanja na području torasemida, iznenađujuće smo pronašli novi do danas nepoznat postupak za pripravu modifikacije I torasemida. Novi postupak za pripravu modikacije I torasemida uključuje pripravu modifikacije I torasemida direktno zakiseljavanjem alkalnog ekstrakta izvorne reakcijske smjese zadnje faze sinteze torasemida. Postupak priprave ovog izuma omogućuje efikasniju, bržu i ekonomski prihvatljiviju metodu za pripravu modifikacije I torasemida.

Prema postupku izuma za pripravu alkalnog ekstrakta izvorne reakcijske smjese zadnje faze sinteze torasemida mogu se upotrijebiti vodene otopine alkalnih hidroksida, kao sto su otopine litij, natrij i kalij-hidroksida kao i vodene otopine alkalnih karbonata, kao što su otopine natrij i kalij-karbonata.

Zakiseljavanje alkalnog ekstrakta izvorne reakcijske smjese zadnje faze sinteze torasemida može se, prema postupku izuma, provesti anorganskim kiselinama, kao što su kloridna, sulfatna, fosfatna i nitratna kiselina te organskim kiselinama, kao što su mravlja, octena, propionska, oksalna, vinska, metansulfonska i *p*-to-luensulfonska kiselina te ugljičnim dioksidom.

Zakiseljavanje alkalnog ekstrakta izvorne reakcijske smjese zadnje faze sinteze torasemida provodi se kontinuiranim dodatkom kiseline dok se ne postigne pH od oko 8,5 do oko 5,0, najbolje od oko 7,5 do oko 7,0, uz miješanje pri brzini mješalice od 10 do 300 o/min, tijekom 5 minuta do 24 sata, što ovisi o koncentraciji kiseline/baze kao i o veličini šarže, volumenu, izvedbi i geometriji reaktora. Tijekom dodavanja kiseline nije potrebno izbjegavanje lokalnih visokih koncentracija kiseline. Zakiseljavanje se provodi pri temperaturama od oko 0°C do oko 50°C, najbolje pri sobnoj temperaturi.

Nakon postizanja željenog pH suspenzija se miješa još od 10 do 240 minuta radi dovršetka kristalizacije i pri temperaturama od oko 0°C do oko 50°C, najbolje pri sobnoj temperaturi. Kristali se iz vodenog medija izdvoje uobičajenim načinom kao što je filtracija, a potom se suše do niskog sadržaja vlage, najbolje do ispod 0,5 %.

Utvrđeno je da primjenom postupka izuma ne dolazi do raspada torasemida, da postupkom izuma modifikacija I torasemida sadrži ostatna otapala unutar farmakopejskih granica, a onečišćenja eventualno prisutna u alkalnom ekstraktu izvorne reakcijske smjese zadnje faze sinteze torasemida postupkom izuma prelaze u lugove, tj. dobiva se kemijski čista modifikacija I torasemida.

Dodatno je utvrđeno da se stabilna modifikacija I torasemida pripravljena prema postupku izuma dobiva u "free flow" formi, tj. pogodnoj za izradu farmaceutskih oblika kao što su tablete, kapsule ili injekcije.

Ovaj izum je ilustriran sljedećim primjerima, koji ga ne ograničavaju ni u kom pogledu.

Primjer 1

Izvorna reakcijska smjesa zadnje faze sinteze torasemida (polazeći od 100 g 4-hidroksi-3-piridinsulfonske kiseline) obradi se s oko 10 %-tnom vodenom otopinom natrijeve lužine. U lužnatu otopinu se kontinuirano doda oko 10 %-tna vodena otopina octene kiseline do pH 7,0 tijekom 30 minuta pri sobnoj temperaturi uz brzinu miješanja od oko 50 o/min. Potom se dobivena suspenzija miješa daljnjih 30 minuta pri istoj temperaturi. Kristali se odsišu i operu s vodom te se nakon sušenja u vakuum sušnici do konstantne mase dobije 100 g modifikacije I torasemida.
Sadržaj HPLC 99,2 %, vlaga < 0,2 %.
IR spektar i rentgenogram praha ovako dobivenog uzorka modifikacije I torasemida odgovaraju IR spektru i rentgenogramu praha autentičnog uzorka modifikacije I torasemida dobivenom prema *Acta Cryst.* **B34**, (1978) 1304-1310.

Primjer 2

Izvorna reakcijska smjesa zadnje faze sinteze torasemida (polazeći od 10,0 kg 4-hidroksi-3-piridinsulfonske kiseline obradi se s oko 2,5 %-tnom vodenom otopinom natrijeve lužine. U otopinu se doda oko 5 %-tna vodena otopina kloridne kiseline do pH 7,1-7,2 tijekom 60 minuta pri sobnoj temperaturi uz brzinu miješanja od oko 200 o/min. Potom se dobivena suspenzija miješa daljnjih 60 minuta pri istoj temperaturi. Kristali se odsišu i operu s vodom te se nakon sušenja u vakuum sušnici do konstantne mase dobije 11,0 kg stabilne modifikacije I torasemida.
Sadržaj HPLC 99,1 %, vlaga 0,3 %.

IR spektar i rentgenogram praha ovako dobivenog uzorka modifikacije I torasemida odgovaraju IR spektru i rentgenogramu praha autentičnog uzorka modifikacije I torasemida dobivenom prema *Acta Cryst.* **B34**, (1978) 1304-1310.

PATENTNI ZAHTJEVI:

1. Postupak za pripravu modifikacije I torasemida **naznačen time** da se alkalni ekstrakt izvorne reakcijske smjese zadnje faze sinteze torasemida podvrgne kontroliranom zakiseljavanju s anorganskim ili organskim kiselinama.
2. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time** da je modifikacija I torasemida kemijski čista.
3. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da modifikacija I torasemida sadrži manje od 0,5 % vode.
4. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da modifikacija I sadrži ostatna otapala unutar farmakopejskih granica.
5. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se za pripravu alkalnog ekstrakta izvorne reakcijske smjese zadnje faze sinteze torasemida koriste vodene otopine litij, natrij i kalij-hidroksida kao i vodene otopine natrij i kalij-karbonata.
6. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se za zakiseljavanje alkalnog ekstrakta izvorne reakcijske smjese zadnje faze sinteze torasemida koriste anorganske kiseline, kao kloridna, sulfatna, fosfatna ili nitratna, odnosno organske kiseline, kao mravlja, octena, propionska, oksalna, vinska, metansulfonska ili *p*-toluensulfonska kiselina.
7. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se za zakiseljavanje alkalnog ekstrakta izvorne reakcijske smjese zadnje faze sinteze torasemida koristi ugljični dioksid.
8. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se zakiseljavanje provodi do pH od oko 8,5 do oko 5,0.
9. Postupak za pripravu modifikacije I torasemida prema zahtjevu 8, **naznačen time**, da se zakiseljavanje provodi do pH od oko 7,5 do oko 7,0.
10. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se zakiseljavanje provodi pri brzini miješalice od 10 o/min. do 300 o/min.
11. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se zakiseljavanje provodi tijekom 5 minuta do 24 sata.
12. Postupak za pripravu modifikacije I torasemida prema zahtjevu 11, **naznačen time**, da se zakiseljavanje provodi kontinuirano.
13. Postupak za pripravu modifikacije I torasemida prema zahtjevima 11 i 12, **naznačen time**, da se zakiseljavanje provodi bez izbjegavanja lokalnih visokih koncentracija kiseline.
14. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se zakiseljavanje provodi pri temperaturama od 0°C do 50°C.
15. Postupak za pripravu modifikacije I torasemida prema zahtjevu 14, **naznačen time**, da se zakiseljavanje provodi pri sobnoj temperaturi.
16. Postupak za pripravu modifikacije I torasemida prema zahtjevu 1, **naznačen time**, da se suspenzija dobivena nakon zakiseljavanja i postizanja željenog pH miješa od 10 minuta do 240 minuta.
17. Postupak za pripravu modifikacije I torasemida prema zahtjevu 16, **naznačen time**, da se suspenzija dobivena nakon zakiseljavanja i postizanja željenog pH miješa pri temperaturama od 0°C do 50°C.
18. Postupak za pripravu modifikacije I torasemida prema zahtjevu 17, **naznačen time**, da se suspenzija dobivena nakon zakiseljavanja i postizanja željenog pH miješa pri sobnoj temperaturi.